made for examination purposes. The Office Action further states that if the elected species is found allowable, the United States Patent and trademark Office will continue the search to the extent necessary to determine the patentability of the generic claim.

The Office Action has rejected Claims 1-16 and 40-51 under 35 U.S.C. §103 (a) as defining subject matter which is allegedly rendered obvious by the teachings in U.S. Patent No. 4,957,927 to Ferrand, et al. (Ferrand, et al.") in view of U.S. Patent No. 4,908,365 to Buzas, et al. ("Buzas, et al.").

Applicants have amended Claim 1 and added Claims 52-59, which, when considered with the comments herein are deemed to place the present case in condition for allowance. Favorable consideration is respectfully requested.

The Office Action alleges that the subject matter in Claims 1-51 are generic to a plurality of patentably distinct species and has requested applicants to elect a single disclosed compound.

Pursuant to the requirement for species election, in the Office Action, applicants elect, with traverse, the species identified as TH-1177, depicted on Page 39 of the instant specification.

Applicants request clarification of the Office Action. Although the Office Action alleges that the action is not a restriction requirement, it involves 35 U.S.C. §121 and 37 C.F.R. §1.142(b) which are sections of the statute and regulations which relate to restriction requirements. Further, it has withdrawn Claims 17-39 form consideration, as if it were a restriction requirement.

If this action is not a restriction requirement, applicants respectfully submit that this section can be ignored. However, assuming pro arguendo, that this action is a restriction requirement, applicants submit the following remarks.

If this is a restriction requirement applicants reserve the right to file a divisional application directed to the non-elected subject matter.

However, applicants hereby traverse the Examiner's requirement for restriction and request reconsideration in view of the following Remarks.

Applicants also respectfully request that this Restriction Requirement be withdrawn since it is not in compliance with 35 U.S.C. §121 and 37 C.F.R. §§1.141-1.142. 35 U.S.C. §121 provides that the Commissioner may restrict an application when "two or more independent and distinct invention are claimed in a single application." (Emphasis added). Similarly, 37 C.F.R. §141(a) permits restriction conditioned upon a finding that independent and distinct inventions are found within one application. Neither of the statutory requirements that the various species are independent or distinct have been proffered as the basis for the requirement of restriction.

Thus, the Office Action has not shown that the various species are independent and distinct. In fact, it has not even alleged that these alleged various patentably distinct species are independent and distinct. Consequently, it has not made out a prima facie case.

Moreover, since the purpose for the election is to further restrict the present application, the election of species is also not in compliance with MPEP §808. MPEP §808 states:

> Every requirement to restrict has two aspects: (a) the reasons (as distinguished from the mere statement of conclusion) why the invention as claimed are either independent or distinct and (b) the reasons for insisting

upon restriction therebetween.

The Office Action, with respect to the election of species, merely concludes that the species are patentably distinct. It did not provide any reasons why the species are patentably distinct. In addition, it has not provided any reasons for insisting upon restriction therebetween.

Thus, this is a restriction requirement, the Office Action has not complied with the statute, regulations or the MPEP. Therefore, the restriction requirement is improper.

It is vital to all applicants that restriction requirements issue only with the proper statutory authorization, because patents issuing on divisional applications which are filed to prosecute claims that the Examiner held to be independent and distinct can be vulnerable to legal challenges alleging double patenting. The third sentence of 35 U.S.C. §121, which states that a patent issuing on a parent application "shall not be used as a reference" against a divisional application or a patent issued thereon, does not provide comfort to applicants against such allegations. The Court of Appeals for the Federal Circuit has declined to hold that 35 U.S.C. §121 protects a patentee from an allegation of same-invention double patenting, Studiengesellschaft Kohle mbH v. Northern Petrochemical Co., 784 F.2d 351, 355, 228 U.S.P.Q. 837, 840 (Fed. Cir. 1986); and in Gerber Garment Technology Inc. v. Lectra Systems Inc., 916 F.2d 683, 16 U.S.P.Q. 2d 1436 (Fed. Cir. 1990), that court held that §121 does not insulate a patentee from an allegation of "obviousness-type" double patenting, and in fact affirmed the invalidation on double patenting grounds of a patent that had issued from a divisional application filed following a restriction requirement. Furthermore, it is far from clear that the step of filing a terminal disclaimer is available to

resolve a double patenting issue that arises after the issuance of a patent on the divisional application.

All these considerations indicate that the imposition of a restriction requirement with inadequate authority can lead to situations in which an applicant's legitimate patent rights are exposed to uncertainty and even extinguished. Accordingly, to protect a patentee's rights and to serve the public's interest in the legitimacy of issued patents, applicants respectfully urge the Examiner not to require restriction in cases such as the present application wherein various aspects of a unitary invention are claimed.

In addition, the Courts have recognized the advantages to the public interest to permit patentees to claim all aspects of their invention, as the applicants have done herein, so as to encourage the patentees to make a more detailed disclosure of all aspects of their invention. The CCPA has observed:

> We believe that the constitutional purpose of the patent system is promoted by encouraging applicants to claim, and therefore to describe in the manner required by 35 U.S.C. §112 all aspects of what they regard as their invention, regardless of the number of statutory classes involved. (Emphasis added).

In re Kuehl, 456, F.2d 658, 666, 177 USPQ 250, (CCPA 1973).

Furthermore, applicants respectfully request that in view of increased Official Fees and the potential limitation of applicants' financial resources, a practice which arbitrarily imposes a Restriction Requirement may become prohibitive, and thereby contravenes the constitutional intent to promote and encourage the progress of science and the useful arts.

Hence, it is respectfully requested that the Examiner reconsider and withdraw the Restriction Requirement, and provide an action on the merits with respect to all of the claims.

Claim 1 has been amended to correct an obvious typographical error. Claims 10 and 20 have been amended to change dependency thereof.

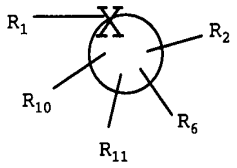
In addition, Claims 42-59 have been added. Support thereof is found throughout the specification, for example, see Page 3, Lines 25 and Page 15, Lines 15-32 and Page 24, Line 1 to page 25, Line 4 of the specification.

No new matter has been added to the specification.

Attached hereto is a marked up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made"

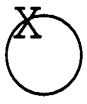
Pursuant to the rejection of Claims 1-16 and 40-51, the Office Action cites Ferrand, et al. in combination with Buzas, et al.

The present invention is directed, inter alia, to a compound of the formula



and pharmaceutically acceptable salts thereof wherein

X is N or CH;



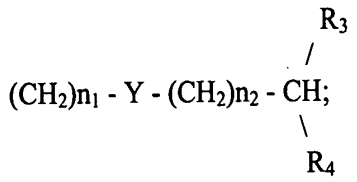
is a cyclic 5-10 membered cyclic ring which

is saturated and which may contain 1 or 2 additional ring heteroatoms selected from the group consisting of O, S and N, with the remaining ring atoms being carbon atoms;

R_1 is (CH_2) n – Z –(R_5), Q, hydrogen or lower alkyl;

R_2 is hydrogen or Q;

Q and Q' may be the same or different and are independently



Z is a chemical bond, CH_2, O, S or NH;

Y is CH_2, O, S or NH;

R_3, R_4, and R_5 are independently cyclic rings containing 6-14 ring carbon atoms, and containing no hetero ring atoms, which cyclic rings may be completely saturated, partially unsaturated or aromatic, and which are unsubstituted or substituted with an electron donating group or electron withdrawing group;

R_3 and R_4 may be fused to form a cyclic ring structure containing 12-28 carbon atoms;

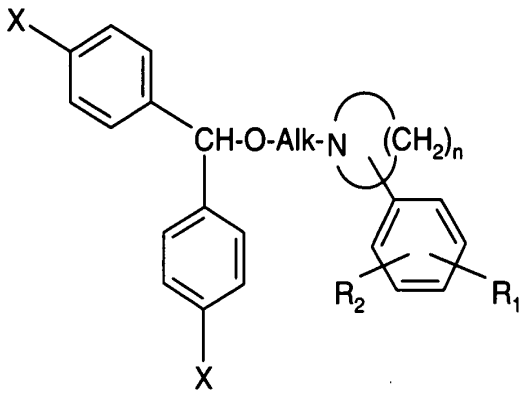
R_6, R_{10} and R_{11} are independently hydrogen or lower alkyl, which is unsubstituted or substituted with an electron withdrawing group or electron donating group;

n_2 is 0-8; and

n and n_1 are independently 1-8, provided that either R_1 is Q or R_2 is Q'.

It is also directed inter alia, to pharmaceutical compositions containing the above-identified compound in association with a pharmaceutical carrier, and to the use of these compounds, for inhibiting cancer cell proliferation in a mammal and to a method for treating cancer in a mammal. In addition, the subject matter of the rejected claims is directed, inter alia, to the use of an organic calcium blocker to treat cancer.

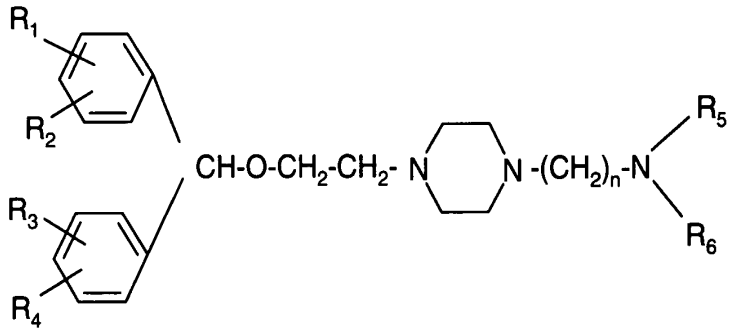
Ferrand, et al. disclose 1-[(diarylmethoxy)alkyl]pyrrolidines and piperidines represented by the following formula:



wherein X is hydrogen or a fluorine atom, Alk is a linear-chain or branched alkyl group having two or three carbon atoms; R_1 and R_2 are hydrogen or a linear-chain or branched alkoxy radical having 1 to 4 carbon atoms; and n is 4 or 5.

The compounds are alleged to be used as cardiovascular medicines.

Buzas, et al. disclose benzhydryloxyethylpiperazine derivatives which correspond to the following general formula:



in which

R_1, R_2, R_3 and R_4 independently of one another represent a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group or the trifluoromethyl group;

n is an integer between 1 and 6 inclusive; and

R_5 and R_6 represent in one case a hydrogen atom and in the other a substituted or unsubstituted benzoyl group, or

R_5 and R_6 form, with the nitrogen atom to which they are bonded, a substituted or unsubstituted 5-membered or 6-membered heterocyclic group selected from the following groups: succinimidyl, 4-phenyl-succinimidyl, phthalimidyl, naphthalimidyl, phthalimidinyl, 3-hydroxyphthalimidinyl, 2-oxobenzimidazolinyl, 3-benzyl-2-oxobenzimidazolinyl, 1,2,3,4-tetrahydro-2,4-dioxoquinazolinyl, 3,4-dihydro-4-oxoquinazolinyl, 3,4-dihydro-4-oxo-2-methyl-quinazolinyl, 3,7-dihydro-1,3-dimethyl-2,6-dioxo-1H-purinyl and 3,7-dihydro-3,7,dimethyl-2,6-dioxo-1H-purinyl.

The compounds are alleged to have an antihistaminic activity without a sedative component.

Neither Ferrand, et al. nor Buzas, et al. disclose that the compounds therein are useful for a method of inhibiting cancer cell proliferation in a mammal or the method of treating cancer, the subject matter of Claims 42-48 and 51. Ferrand, et al. disclose that the compounds therein are useful as cardiovascular medicines, while Buzas, et al. disclose that the compounds therein have antihistaminic activity. A thorough review of both references clearly reveals that neither references discloses or suggests that the compounds therein are useful for treating cancer or inhibiting cancer cell proliferation. In fact, cancer is not even mentioned in either reference. Thus, Ferrand, et al. and Buzas, et al. in combination do not teach, disclose or suggest the methods recited in Claims 42-48 and 51. Thus, the references in combination do not render obvious the subject matter therein.

Moreover, the references in combination do not teach, disclose or suggest the remaining subject matter in the rejected claims.

In fact, applicants respectfully submit that the references are not combinable in the first instance. Case law has held that obviousness cannot be established by combining the

teachings of the prior art absent some teaching or suggestion to do so. ACS Hospital Systems, Inc. v. Montefiore Hospital, 72 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984).

As stated by the Federal Circuit, In re Rouffet, 149 F.3d 1350, 1355-1356, 47 USPQ2d 1453,1456 (Fed. Cir. 1998),

> When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. See In re Geiger, 815 F2d 686, 688 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Although the suggestion to combine references may flow from the nature of the problem, see Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F3d 1568, 1573 37 USPQ2d 1626, 1630 (Fed. Cir. 1996), the suggestion more often comes from the teachings of the pertinent references, see In re Sernaker, 702 F2d 989, 994, 217 USPQ 1, 5 (Fed. Cir. 1983), or from the ordinary knowledge of those skilled in the art that certain references are of special importance in a particular field see Pro-Mold, 75 F3d at 1573 (citing Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F2d 281, 297 n.24, 227 USPQ 657, 667 n.24 (Fed. Cir. 1985)). Therefore, "[w]hen 'determining the patentability of a claimed invention which combines two known elements, "the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'" See In re Beattie, 974 F2d 1309, 1311-12, 24 USPQ2d 1040, 1042 (Fed. Cir. 1992) (quoting Lindenmann Maschinenfabrik GmbH v. American Hoist & Derrick Co., 730 F2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984).

Just because the prior art references asserted by the Office Action are directed to pharmaceuticals, this in and of itself is insufficient to provide the proper motivation or

suggestion to combine the references. When determining the patentability of a claimed invention which combines two elements, the question is whether there is something in the prior art to suggest the desirability and thus the obviousness of making the combination. See, In re Rouffet, 149 F3d at 1356, 47 USPQ 2d at 1456.

Moreover, as stated by the Court,

> Obviousness is determined from the vantage point of a hypothetical person having ordinary skill in the art to which the patent pertains. See 35 U.S.C. §103(a). This legal construct is akin to the "reasonable person" used as a reference in negligence determinations. The legal construct also presumes that all prior art references in the field of the invention are available to this hypothetical skilled artisan. See In re Carlson, 983 F2d 1032, 1038, 25 USPQ2d 1207, 1211 (Fed. Cir. 1993).
>
> As this court has stated, "virtually all [inventions] are combinations of old elements." Environmental Designs, Ltd. v. Union Oil Co., 713 f2D 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983); see also Richdel, Inc. v. Sunspool Corp., 714 F2d 1573, 1579-80, 219 USPQ 8, 12 (Fed. Cir. 1983)("Most, if not all, inventions are combinations and mostly of old elements."). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of every claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed invention itself is a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriaate process by which to determine patentability." Sensonics, Inc. v. Aerosonic Corp., 81 F3d 1566, 1570, 38 USPQ2d 1551, 1554 (Fed. Cir. 1996).
>
> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same

> problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

In re Rouffet, 149 F3d at 1357, 47 USPQ2d 1457-1458.

In making a prima facie case for an obviousness rejection under 35 U.S.C. §103, the Office Action must point to specific information in the prior art references that suggest combining the references. See In re Dembiczak, 175 F3d 994, 1000, 50 USPQ 2d 1614, 1618 (Fed. Cir. 1999). It is required to explain, when analyzing the prior art, what specific understanding or technical principle would have suggested the combination. Rouffet, 149 F3d at 1357, 47 USPQ2d at 1450.

The Office Action failed to provide any such information. It failed to identify the motivation to combine. It merely alleges that the compounds in Ferrand, et al. differ from the claimed invention in the cyclic linking group, and alleges that Buzas teach analogous compounds having N-heterocyclic linking groups. It thus makes an overall conclusion without identifying the rationale for the combination. It did not point to any specific information in the prior art references that suggested combining the references.

However, the subject matter in Ferrand, et al. and Buzas, et al. are patentably distinct. In the first instance, as indicated hereinabove, the utilities are different. Moreover, the compounds therein are structurally non-similar. For example, the heterocyclics in the main chain are patentably distinct, in Ferrand, et al., the heterocyclic moiety is a pyrrolidine or piperidine, i.e., heterocyclics having one nitrogen ring atom, while in Buzas, et al. related to piperazine derivatives, i.e., heterocyclic having two nitrogen rig atoms. Moreover, the substituents on the heterocyclic rings are structurally non-similar. In Ferrand, et al. the substituent is a phenyl ring, while in Buzas, et al., the substituent is $(CH_2)_n$-NR_5R_6, which

group is quite different from phenyl. Thus, because the compounds in the cited prior art references are patentably distinct and the uses are quite different there, is no reason why one of ordinary skill in the art would combine the teachings therein.

Further, the Office Action failed to make any specific finding concerning the level of ordinary skill in the art, the nature of the problem to be solved or any other factual finding that might serve to support an obviousness rejection, as required in a proper '103 rejection. Dembiczak, 175 F3d at 1000, 50 USPQ2d at 1618.

Thus, the Office Action failed to provide the appropriate bases or motivation that suggests combining the references in the manner that it did, as required in support of a rejection under 35 U.S.C. §103 for a combination of prior art references.

Combining the prior art reference without evidence of such a suggestion, teaching or motivation takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability. This is the essence of hindsight which is impermissible, In re Gorman, 933 F2d 982, 987, 18USPQ 1885, 1888 (Fed. Cir. 1990), and in which the United States Patent and Trademark Office has engaged. Inasmuch as the Office Action failed to provide the appropriate evidence of a suggestion, teaching or motivation to combine the prior art references, it is respectfully submitted that the Office Action did not make out a prima facie case of obviousness.

Thus, inasmuch as the Office Action has failed to make a prima facie case of obviousness with respect to the subject matter in Claims 1-16 and 40, 41, 49 and 50, the subject matter in these rejected claims have not been rendered obvious by the teachings in Ferrand, et al. and Buzas, et al.

Therefore, in view of the comments hereinabove, the rejection of Claims 1-16 and 40-51 under 35 U.S.C. §103(a) is obviated; withdrawal thereof is respectfully requested.

Therefore, in view of the amendment to the claims and the remarks herein, it is respectfully submitted that the present case is in condition for allowance. Favorable action is respectfully requested.

Respectfully submitted,

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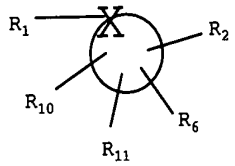
MJC/bb

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Please amend Claim 1 as follows:

1. (Amended) A compound of the formula:



and pharmaceutically acceptable salts thereof wherein

X is N or CH;

is a cyclic 5-10 membered cyclic ring which

is saturated and which may contain 1 or 2 additional ring heteroatoms selected from the group consisting of O, S and N, with the remaining ring atoms being carbon atoms;

R_1 is (CH_2) n – Z –(R_5), Q, hydrogen or lower alkyl;

R_2 is hydrogen or Q' [Q];

Q and Q' may be the same or different and are independently

$$(CH_2)n_1 - Y - (CH_2)n_2 - \underset{\displaystyle R_4}{\overset{\displaystyle R_3}{CH}};$$

Z is a chemical bond, CH_2, O, S or NH;

Y is CH_2, O, S or NH;

R_3, R_4, and R_5 are independently cyclic rings containing 6-14 ring carbon atoms, and containing no hetero ring atoms, which cyclic rings may be completely saturated, partially unsaturated or aromatic, and which are unsubstituted or substituted with an electron donating group or electron withdrawing group;

R_3 and R_4 may be fused to form a cyclic ring structure containing 12-28 carbon atoms;

R_6, R_{10} and R_{11} are independently hydrogen or lower alkyl, which is unsubstituted or substituted with an electron withdrawing group or electron donating group;

n_2 is 0-8; and

n and n_1 are independently 1-8, provided that either R_1 is Q or R_2 is Q'.

10. (Amended) The compound according to [any one of] Claim[s] 7[,8 or 9] wherein R_3 and R_4 are independently aromatic rings.

20. (Amended) The compound according to Claim 17[, 18 or 19] wherein R_3 and R_4 are independently aromatic.

Please add Claims 52-59 as follows:

52. (New) The compound according to Claim 1 wherein X is CH.

53. (New) The compound according to Claim 1 wherein X is N.

54. (New) The pharmaceutical composition according to Claim 41 wherein X is CH.

55. (New) The pharmaceutical composition according to Claim 41 wherein X is N.

56. (New) The method according to Claim 42 wherein X is CH.

57. (New) The method according to Claim 42 wherein X is N.

58. (New) The method according to Claim 47 wherein X is CH.

59. (New) The method according to Claim 47 wherein X is N.